REMARKS

The specification and pending claims of the application have been amended to correct errors and in connection with objections taken by the Examiner. No new matter has been added by the amendments. The changes made to the specification and claims by the current amendment, including deletions and additions, are shown herein with ~~deletions~~ designated with a strikethrough and <u>additions</u> underlined.

The title and figure legends have been amended in accordance with the Examiner's objections thereto. The "Cross-reference to Related Applications" section at the beginning of the specification has been amended to correct errors in dates given in the application as filed. Claims 1, 2, and 5-15 have been amended in response to objections thereto.

The following changes have been made that are not in connection with matters raised by the Examiner:

> The preambles of claims 1 and 14 have been amended to recite that the protein is "an anti-microbial protein"; and
>
> The recitation in claim 14 "...expression of said protein, said protein selected from..." has been amended to read "...expression of said protein, wherein said protein is selected from..."

The first of these changes has been made to bring the claims into conformity with the description of the invention as a whole from which it is abundantly clear that the subject proteins are anti-microbial proteins. The amendment in no way therefore constitutes the addition new matter. The second amendment has been made merely to improve the language of the claim.

In addition, new Claims 16-22 have been added. Support for the limitations of part (ii) of claim 16 can be found at page 7, lines 10-15 and at page 10, lines 29-31. Support for Claims 17-18 can be found at page 7, lines 14-15. Support for Claim 19 can be found at page 11, line 2-5. Support for Claim 20 can be found at page 7, lines 16-18. Claims 21 and 22 include different combinations of limitations found in Claims 17-20.

<u>I. Status of the claims</u>

Claims 1-22 are now pending in the application.

Applicants also acknowledge that claims 3 and 4 have been withdrawn from consideration. Applicants further acknowledge that rejoinder of claims 3 and 4 will be

considered on allowance of claims 1, 5 and/or 14 as linking claims. As argued in the response filed December 26, 2003 to Paper No. 7, MPEP 809.03 and 809.04 require that the restriction be withdrawn on allowance of the linking claims.

II. Objections to the title, abstract and specification

In paragraph 2 of the Action, the Examiner has kindly pointed to errors in the cross-references to related application at the beginning of the specification and indicated that the application does not comply with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. The errors in the cross-references have been corrected by the amendments referred to above. Applicants respectfully submit that the application now complies with all conditions for receiving an earlier filing dated under 35 U.S.C. 120.

In paragraph 3 of the Action, the Examiner has objected to the application for failure to comply with the requirements of 37 CFR 1.821 through 1.825. Specifically, the Examiner maintains that sequence identifiers are required in either the legend or the brief description of Figure 6.

Applicants have amended the brief description of Figure 6 at page 5 of the specification to incorporate the relevant sequence identifiers rendering the objection moot.

The Examiner, in paragraph 4 of the Action, has objected to the abstract as not being descriptive of the invention. A replacement abstract which is descriptive of the invention as claimed is submitted herewith.

In paragraph 5 of the Action, the Examiner has objected to the title as not being descriptive of the instant invention. In response to this objection, the title has been replaced with a title that is consistent with the claimed subject matter.

The section title at line 28, page 5, of the specification has been replaced in connection with the objection taken in paragraph 6 of the Action. Applicants submit that in view of this amendment, the disclosure now conforms to MPEP 608.01(a) and (g).

In paragraph 7 of the Action, the Examiner has objected to the brief description of Figure 12 in that it does not include the information on the figure given at page 30, lines 4-8 of the specification. The amendments include an amendment to incorporate the page 30, lines 4-8, disclosure into the Figure 12 description at page 5.

III. Objections to the claims

In paragraph 8 of the Action; the Examiner has objected to claims 1-2 and 5-15 because of the following informalities.

In claims 1 and 14, part (i), "(SEQ ID NO:1)" should be replaced with --SEQ ID NO:1--.

In claim 1, part (ii), claim 5, line 1, and in claim 6, line 1, "includes" should be replaced with--comprises--.

Claims 2, 6-7, 9, 11-13 and 15 lack an article at the start of the claim.

Claims 5, 8 and 10 have an improper article before "DNA" in line 1.

In claim 13, line 3, "soybeans" should be singular to be consistent with the other members of the group.

In connection with these objections, the following amendments have been made:

- the parentheses have been removed from around the sequence identifiers in part (i) of claims 1 and 14;
- the words "which includes" have been replaced with "comprising" in claims 1, 5 and 6;
- an article has been added at the beginning of claims 2, 6-7, 9, 11-13 and 15;
- the indefinite article before "DNA" in claims 5, 8 and 10 has been replaced with a definite article; and
- in claim 13, "soybeans" has been replaced with "soybean".

In view of the foregoing amendments, withdrawal of the objection to the claims is warranted.

IV. Rejections under 35 U.S.C. §112, first paragraph

The Examiner, in paragraph 10 of the Action, has rejected claims 1, 5 and 7 under 35 U.S.C. 112, first paragraph, as "containing matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention". In connection with claim 7, the Examiner contends that "the specification does not disclose a repeatable process to obtain the plasmids [pPCV91-MiAMP1 and pET-MiAMP1] and it is not apparent if the plasmids are readily

available to the public". The Examiner further contends that a deposit [of the plasmids] is required for enablement purposes. Applicants respectfully disagree.

The construction of pPCV91-MiAMP1 is detailed in Example 12 at page 23 of the specification. A map of the plasmid is also given in Figure 8. It is abundantly clear from Example 12 that:

- the plasmid was constructed by ligating MiAMP1 DNA into the plasmid pPCV91;
- the endonucleases used for excising the MiMP1 DNA and opening pPCV91 are provided; and
- the ligating step is also described.

The source of pPCV91 is provided in the example and a construct comprising the MiAMP1 DNA is detailed in Example 11. From this information, one of even less than ordinary skill in the art would be able to construct pPCV91-MiAMP1.

Example 14 provides detail of the construction of pET-MiAMP1. The construct is also depicted in Figure 9. In this instance, the plasmid can be prepared by ligating MiAMP1 DNA into the commercially-available expression vector pET-17b after *NdeI*/*Bam*HI cleavage. The preparation of pET-MiAMP1 would therefore be a routine procedure for one of ordinary skill in the art.

Contrary to the Examiner's assertion, the specification does describe a repeatable process for the preparation of pPCV91-MiAMP1 and pET-MiAMP1 so deposits of these plasmids are not required. Should the Examiner nevertheless find the foregoing comments unpersuasive, Applicants respectfully suggest that the Examiner should specify in any further Action what additional information would be required by a person of ordinary skill in the art to prepare the subject plasmids.

In paragraph 11, the Examiner has rejected claims 1, 5 and 7-15 under 35 U.S.C. 112, first paragraph, on the basis that the specification 'does not reasonably provide enablement for any nucleic acid encoding a protein comprising amino acids 27-102 of SEQ ID NO:1, encoding a "variant" or "homologue" of that protein, or encoding any *Protoceae* [*sic*] protein that reacts with any antibody to a protein comprising amino acids 27-102 of SEQ ID NO:1, constructs comprising the nucleic acids, and cells, plants and reproductive material comprising the constructs'. The Examiner further asserts that the "specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims".

The Examiner correctly notes that the specification provides numerous examples relating to MiAMP1. However, the Examiner contends that the specification 'fails to provide guidance for construction or isolation of the nucleic acids encoding a "variant" or "homologue" of a protein comprising amino acids 27-102 of SEQ ID NO: or encoding a *Protoceae* [*sic*] protein that reacts with an antibody to a protein comprising amino acids 27-102 of SEQ ID NO:1'. The Examiner supports this contention by stating that "[f]or example, exact hybridization or PCR amplification conditions and probes/primers to use in isolation of nucleic acids other than SEQ ID NO:2 are not taught".

We draw the Examiner's attention to the fact that a homologue of MiAMP1 is defined in the instant applicant as being: a protein having substantially the same amino acid sequence as the Figure 6 protein, which means that the majority of MiAMP1 residues will be present in a homologue at the same relative positions (see specification at page 10, line 29 to page 11, line 6). At the end of the cited passage, it is indicated that "cysteine and histidine residues can rarely be substituted". At page 11, lines 7 to 14 a variant of MiAMP1 is defined. Specifically, it is stated that homologues include engineered variants in which particular residues have been replaced or there have been deletions. It is nevertheless clear from the definition that a variant MiAMP1 still has substantially the same amino acid sequence as MiAMP1 with the majority of residues still present in the same relative positions.

Due to the close identity between a homologue or variant of the subject anti-microbial protein and MiAmp1, the procedures used to

isolate and purify MiAMP1;

test the activity of MiAMP1;

isolate or synthesize DNA encoding MiAMP1;

prepare constructs comprising DNA encoding MiAMP1; and

transform plant cells with the foregoing constructs;

would also be applicable to homologues and variants of MiAMP1. Thus, for example, the person of skill in the art would immediately appreciate from the teachings of the instant specification that the hybridization or PCR amplification conditions and probes/primers used for

the isolation of SEQ ID NO: 2 DNA would also be applicable to homologues and variants of MiAMP1.

The Examiner suggests in the first full paragraph at page 8 of the Action that the specification is deficient in that it fails to teach that a Greek key β-barrel makes up the major structural element of MiAMP1 and that mutations that disrupt this structure would likely destroy the protein's ability to function as an anti-microbial protein. The Examiner then asserts that the specification fails to provide guidance for the construction of variants and homologues within the full scope of the claims. Applicants reiterate that it is indicated in the specification that substitution of cysteine and histidine residues should be avoided. It is also indicated that residues in a homologue should be present at the same relative positions as in MiAMP1. Consequently, following the instructions given in the specification when designing, for example, an MiAMP1 variant, would direct one of skill in the art away from destruction of the protein's ability to function as an anti-microbial protein. This direction would result despite the fact that the Greek key β-barrel structural element of MiAMP1 is not disclosed.

The Examiner asserts in the second full paragraph at page 8 of the Action that undue experimentation 'would have been required by one skilled in art to develop and evaluate nucleic acids encoding "variants" and "homologues" of SEQ ID NO:1'. The Examiner suggests that making "all possible single amino acid substitutions in an 102 amino acid long protein ... would require making and analyzing 19^{102} nucleic acids". In no way does the specification teach embarking on such an endeavor nor would a person of ordinary skill in the art make such an interpretation of the disclosure. To the contrary, the specification teaches that "the majority of residues present in MiAMP1 will be present in a homologue in the same relative position to each other" (see page 10, line 30 to page 11, line 1). The specification also teaches selective substitution or deletion of residues with substitutions being based on knowledge of what changes would not be expected to destroy anti-bacterial activity. By following the teachings of the instant specification, the person of ordinary skill in the art would be confronted with no more than a routine amount of work in developing and evaluating nucleic acids encoding variants and homologues of SEQ ID NO: 1.

Contrary to the Examiner's assertion therefore, Applicants submit that the full scope of the claims are enabled when the definition of a homologue and variant of MiAmp1 are taken into account.

In paragraph 12 of the Action, the Examiner has rejected claims 1, 5 and 7-15 under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time that application was filed, had possession of the claimed invention. The Examiner has based this rejection on the fact that the specification only describes a coding sequence from *M. integrifolia* that comprises SEQ ID NO: 2 and variants encoding SEQ ID NOs: 15-21 and the fact that the Applicants do not describe other DNA molecules encompassed by the claims.

It is agreed that the only specific DNA sequences disclosed are SEQ ID NOs: 2 and 15-21. However, as stated in the specification, the invention comprises the identification of a new class of potent anti-microbial protein with MiAMP1 being the prototype of the class. The inventors further demonstrated in Example 10 that homologues of MiAMP1 are abundant in other excisions of the family *Proteaceae*. With the sequence information provided in the specification, DNA encoding those homologues could be isolated and sequenced by a person of ordinary skill in the art as a matter of routine. Hence, by describing how to obtain homologues and variants of MiAMP1, Applicants have provided an adequate written description of the invention as claimed despite there being only the specific DNA sequences given by SEQ ID NOs: 2 and 15-21.

The Examiner refers to the decisions in *Uni. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016. It is noted that in the passages cited from these cases it is indicated that the mere provision of material or naming of material does not provide information on the structural or physical characteristics of the material. Applicants believe that the present application can be distinguished from these cases in that Applicants have provided a prototype molecule that has been sequenced at both the amino acid and nucleic acid levels. Other characteristics of the prototype molecule have also been established. The homologues and variants of the present claims are thus defined by more than just a name since sequence information, activity and other characteristics can be extrapolated from the prototype molecule.

Contrary to the Examiner's assertion therefore, Applicants were in possession of the genus claimed at the time the application was made and respectfully request that the instant rejection of claims 1, 5 and 7-15 under 35 U.S.C. 112, first paragraph, be withdrawn.

V. Rejections under 35 U.S.C. §112, second paragraph

In paragraph 14 of the Action, the Examiner has rejected claims 1-2 and 5-15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

The Examiner asserts that claims 1 and 14 in part (i) thereof are indefinite in their recitation of "an amino acid sequence ...". While not agreeing with this assertion, Applicants have nevertheless deleted "an amino acid sequence corresponding to" from these claims.

The Examiner contends that claims 1 and 14 in part (ii) are indefinite in their recitation of "homologue". As noted above, there is a clear definition in the specification of what constitutes a homologue of the subject anti-microbial protein. When the claims are considered in the light of the specification as a whole, the extent to which and, nature in which, a homologue differs from SEQ ID NO:1 is abundantly clear.

The Examiner similarly contends that claims 1 and 14 in part (iii) are indefinite in their recitation of "variant". As with the term "homologue", what constitutes a variant of MiAMP1 is defined in the specification. Consequently, the extent to which and, nature in which, a variant differs from SEQ ID NO: 1 is clear when the claims are considered in the light of the specification.

The Examiner next asserts that claims 1 and 14 are indefinite through the recitation in part (iv) of each of "specifically reacts" and "essentially the same". With regard to the first recitation, the Examiner will be aware that a characteristic of antibodies is that they react with a high degree of specificity for the antigen to which they have been raised. The specific reaction between the protein isolated from the family *Proteaceae* and an antibody raised against protein (i) of claims 1 and 14 derives from the specificity of the antibody for its antigen. In view of this, Applicants submit that the recitation "specifically reacts" does not render the subject claims indefinite.

The second recitation objected to by the Examiner has been removed from claims 1 and 14.

The Examiner states in paragraph 14 that claim 5 lacks an antecedent basis for "said encoded protein". While not agreeing with this statement, Applicants have amended claim 5 to recite "the protein encoded by said DNA".

The Examiner has objected to claim 12 as being indefinite through the recitation of "forestry". In accordance with the Examiner's suggestion, "forestry" has been replaced with "trees" in the amended claims.

The final objection under 35 U.S.C. 112, second paragraph, is to claims 8 and 10 as being indefinite through the recitation of "harbouring". Again, in accordance with the Examiner's suggestion, "comprising" has been substituted for "harbouring" in the amended claims.

In view of the foregoing comments and the relevant claim amendments, Applicants respectfully request that the 35 U.S.C. 112, second paragraph, rejection of claims 1-2 and 5-15 be withdrawn.

VI. Rejections under 35 U.S.C. §102(b)

The Examiner has rejected claims 1, 5, 8-11 and 13-15 under 35 U.S.C. 102(b) as being anticipated by Terras *et al.* (1995, *The Plant Cell*, Vol. 7, pp. 573-588). The Examiner asserts that Terras *et al.* teach a radish nucleic acid encoding an anti-microbial protein that would be a "variant" or "homologue" of SEQ ID NO: 1. Applicants respectfully disagree.

As indicated above, a homologue of MiAMP1 is defined in the instant applicant as being a protein having substantially the same amino acid sequence as the Figure 6 protein which means that the majority of MiAMP1 residues will be present in a homologue at the same relative positions (see specification at page 10, line 29 to page 11, line 6). At the end of the cited passage, it is indicated that "cysteine and histidine residues can rarely be substituted".

When the radish protein (Rs-AFP1), of Terras *et al.* is considered, it can be seen to be a 52-residue polypeptide in its mature form with two distinctive groupings of cysteine residues. The following sequence begins at residue 15 of the polypeptide:

CGNNNACKNQC

while the following sequence occurs at the carboxy terminus:

CICYFPC

In all there are eight cysteines in the mature Rs-AFP1 polypeptide (see Figure 5C of Terras *et al.*).

The mature MiAMP1 polypeptide consists of 78 residues. Despite being 50% larger than Rs-AFP1, MiAMP1 has only six cysteine residues. Even more striking is the complete absence in MiAMP1 of the cysteine groupings of Rs-AFP1 presented above.

On the basis of cysteine content alone and in view of what constitutes a homologue of MiAMP1, the instant claims do not embrace the Terras *et al.* radish protein.

A variant of MiAMP1 in view of the definition thereof at page 11 of the specification, similarly does not embrace Rs-AFP1. At page 11 it is indicated that homologues include engineered variants in which particular residues have been replaced or there have been deletions (see lines 7-14). Nevertheless, a variant MiAMP1 still has substantially the same amino acid sequence as MiAMP1 with the majority of residues still present in the same relative positions. The definition of a variant of MiAMP1 accordingly excludes Rs-AFP1.

Since the Rs-AFP1 polypeptide sequence does not fall within the scope of the claims of the instant application, the Terras *et al.* disclosure is not an anticipation of any claim. Withdrawal of the 35 U.S.C. 102(b) rejection of claims 1, 5, 8-11 and 13-15 on the basis of the foregoing citation is thus respectfully requested.

VII. Rejections under 35 U.S.C. §103(a)

The Examiner has rejected claims 1, 5 and 8-15 under 35 U.S.C. 103(a) as being unpatentable over Terras *et al.* in view of Gordon-Kamm *et al.* (1990, *The Plant Cell,* Vol. 2, pp. 603-618). The Examiner contends that at the time the invention was made, "it would have been obvious to one of ordinary skill in the art to modify the method of producing pathogen-resistant plants as taught by Terras et al, to transform the nucleic acid into maize as described in Gordon-Kamm et al" and that "[o]ne of ordinary skill in the art would have been motivated to do so because of the economic importance of maize and because of the effectiveness of the nucleic acid when transformed into tobacco".

Applicants have pointed out above that the Terras *et al.* disclosure is not an anticipation of any claim of the instant application. The 35 U.S.C. 103(a) rejection on the basis of Terras *et al.* in view of Gordon-Kamm *et al.* is therefore not legitimate. In any case, modifying the method of Terras *et al.* as taught by Gordon-Kamm *et al.* would still not provide grains, vegetables or oil-seed plants transformed with the nucleic acid of the instant claims.

In view of the foregoing comments, Applicants respectfully request that the objection be withdrawn.

VIII. New Claims

New Claim 16 is limited to DNA's that encode either "(i) a protein comprising residues 27 to 102 of the sequence shown in SEQ ID NO: 1; [or] (ii) a protein having a cysteine content and spacing identical to (i), wherein a majority of amino acid residues are identical to (i), and at the same relative positions as (i)." The Examiner has raised no objections with regard to part (i). Part (ii) of the claim is limited to those specific proteins that retain the cysteine spacing of the wild-type protein. These cysteine residues provide the "disulfide bonds which are critical to maintaining the overall structure of the protein." Specification, page 7, line 14. As such, these recited proteins will "retain the overall three-dimensional shape and overall antimicrobial activity of the protein." Specification, page 7, lines 8-11. The limitations of Claim 16 not only distinguish the recited invention from the prior art, but also are sufficiently definite to meet the requirements of § 112, second paragraph and provide sufficient information of the recited proteins to convey that the Applicants were in possession of the invention in accordance with § 112, first paragraph.

Claims 17-22 provide additional limitations that further distinguish the invention from the prior art, and also further limit the scope of the claims within the scope of the written description. Accordingly, these claims are presented as fully in condition for allowance.

IX. Conclusion

Should there be any further questions regarding the above-captioned patent application, the Examiner is respectfully requested to contact the undersigned agent at the telephone number below. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept. 12, 2003

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